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*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

WO 01/85183 A2

(54) Title: PREPARATION FOR THE PREVENTION AND TREATMENT OF OCULAR DISORDERS

(57) Abstract: The present invention relates to a preparation for the prevention and/or treatment of ocular disorders which comprises: a. an aldose reductase inhibitor; b. an intra ocular pressure lowering component; and c. a component that increases ocular blood flow. Component a can be *Chrysantemum morifolium, Bixa orellana, Ipomoea batatas Vaccinium myrtillus, Buddleia officinalis, Cistancha salsa* or *Glycyrhizza glabra* extract. Component b can be a green tea extract, myrecetin, querecetin or tannin. Component c can be an isoflavon or a water soluble carotenoid.

# Preparation for the prevention and treatment of ocular disorders

The present invention relates to a preparation for the prevention and/or treatment of ocular disorders, in particular cataracts, age-related macula degeneration (AMD) and glaucoma.

Cataracts are opacities of the lens and the onset of the disorder in patients is usually above 50 years of age. The opacities in the lens are aggregates of damaged and hence dysfunctional lens proteins, predominantly crystallines. Two mechanisms are responsible for the damage inflicted on the crystallines: oxidative stress, leading to destruction of the proteins, and high glucose or sorbitol levels of the lens, causing glycosilation of the crystallines, making them dysfunctional.

Excessive exposure of the lens to sunlight, nutrition status and smoking are the main risk factors for oxidative stress of the lens. High glucose and sorbitol levels have been established with diabetes patients. Current methods for the treatment of cataracts include lens extraction, costing about $3.5 billion annually in the USA. Existing nutritional supplement formulae for the prevention of cataracts are usually based on antioxidants (vitamin E, vitamin C, β-carotene) and minerals that support antioxidant proteins (Zn, Se).

Age related macula degeneration (AMD) is a degenerative disorder of the macula lutea or yellow spot, which is the central part of the retina, with the highest visual acuity and concentration of cones. Two forms of AMD can be discriminated. Dry AMD or atrophic AMD is characterized by hard or soft drusen (deposits of cellular debris), changes in the retinal pigment epithelium or atrophy of the photoreceptors and the retinal pigment epithelium. Wet AMD is a more advanced form of AMD and is characterized by neovascularization and exudation of fluid. Two pigments are present in the macula and are responsible for its characteristic yellow color: lutein and zeaxanthin. These water soluble carotenoids are thought to protect the macula by absorbing high energy blue light and by their antioxidant properties. The macula is avascular and depends therefor on the choroid, which is the layer in the eye behind the retina, for its nutrient supply. Current supplement prevention formulae include mostly antioxidants and lutein.

Glaucoma is a collection of disorders which is caused by an increased intra ocular pressure (IOP). This pressure causes ischemic insults to the retina and irreversible damage to the ocular nerve. Common supplements for the prevention of glaucoma are based on antioxidants.

In view of the wide spread occurrence of the above mentioned disorders, there is a need for a preparation that can prevent or treat these disorders simultaneously. The present inventors have now found such a preparation that is particularly active against the above three disorders, cataracts, age related macula degeneration and glaucoma.

The present invention provides a preparation for the prevention and/or treatment of ocular disorders which comprises

a. an aldose reductase inhibitor;
b. an intra ocular pressure lowering component; and
c. a component that increases ocular blood flow.

Component a, the aldose reductase inhibitor limits the reduction of glucose to sorbitol. Preferably this component is a *Chrysanthemum morifolium, Bixa orellana, Ipomoea batatas, Vaccinium myrtillus, Buddleia officinalis, Cistancha salsa or Glycyrhizza glabra* extract.

Extracts from *Chrysanthemum morifolium* are flower extracts and should certainly comprise acacetin, diosmetin, luteoline or their glucosides and/or ellagic acid. The extract is prepared such that it contains 0.25 wt.% chlorogenic acid. Extracts from *Bixa orellana* should certainly comprise gallic acid and/or pyrogallol. Extracts from *Ipomoea batatas* should certainly comprise scopoletin and/or caffeic acid. Extracts of *Vaccinium myrtillus* are berry extracts and contain preferably at least 25 wt.% anthocyanosides (based on dry matter). The extract of *Buddleia officinalis* is preferably an alcohol/water extract of the flower bud. Such extracts can be obtained from the firm KING HERB. The extract of *Cistancha salsa* is preferably an alcohol/water extract of the stem, also available from KING HERB. The extract of *Glycyrhizza glabra* is preferably an extract containing at least 12.7 wt.% glycyrrhizic acid. It can be obtained from ZANDU.

Suitability of the plant (extracts) as aldose reductase inhibitors for the object of the invention can also be determined by means of the assay as described in the examples hereafter. The extract should have an $LC_{50}$ of 0.03 mg/ml at the most.

Consequently, according to the invention, the aldose reductase inhibitor comprises preferably at least a component selected from the group consisting of acacetin, diosmetin, luteoline, ellagic acid, gallic acid, pyrogallol, isoscutellarein, scopoletin, 3,5-dicaffeoylquinic acid and caffeic acid or their functional analogues, said functional analogues being glucosides, esters or salts thereof.

Preferably one or more of these components, in synthetic form but most preferably as extract, are preferably administered in a daily dose of 0.01 to 100 mg/day, preferably 1 to 50 mg/day.

Component b, the intra ocular pressure lowering component is a component selected from the group catechins, flavonoids and/or tannins. Preferably catechins, and most preferably in the form of a green tea extract is used, i.e. an extract rich in epigallocatechin or epigallocatechin gallate. Component b is alternatively myrecetin, quercetin or tannin. Component b is preferably administered in a daily dose of 0.01 to 100 mg/day, preferably 1 to 50 mg/day.

Component c, the component that increases ocular blood flow is an isoflavon or a water soluble carotenoid. The isoflavon is preferably puerarin or an equivalent thereof. This isoflavon can be extracted from the roots of *Pueraria lobata*, also known as kudzu. This extract is traditionally used to assist in alcohol withdrawal support and to prevent or treat angina and high blood pressure. The water soluble carotenoid is preferably crocetin or crocin or an equivalent thereof. Component c is preferably administered in a daily dose of 0.01 to 50 mg/day, preferably 0.1 to 10 mg/day.

The preparation of the invention can further contain, beside the above mentioned components a, b and c, lutein, zeaxanthine and/or one or more antioxidant. Lutein and zeaxanthine can be present in an amount of 0.01 to 50 mg/day, preferably 0.1 to 20 mg/day. Preferably lutein is included, in particular as a stable and readily absorbable form, such as a lutein ester.

Antioxidants can be vitamin C, vitamin E, zinc, β-carotene, copper, and selenium. An extract with antioxidant activity is for instance bilberry extract.

The preparation can also contain one or more of vitamin A, riboflavin, gingko biloba, N-acetylcysteine, vitamin B6, vitamin B12 and folic acid.

The preparation of the invention can be used in the treatment and/or prevention of ocular disorders, in particular in the treatment or prevention of cataracts, age related macula degeneration and glaucoma.

The preparation of the invention is a pharmaceutical or dietary preparation, in particular a nutritional supplement. The nutritional supplement that is administered on a daily basis to prevent the ocular disorders. Such a supplement can have the form of a tablet, drink, powder, bar, cookie, cereal, etc., as is known to the skilled person. Also foods which contain the above ingredients are possible.

Examples

**Assay aldose reductase inhibition**

The inhibitory effects of herbal extracts towards aldose reductase are assessed with the following in vitro assay.

Dl-glyceraldehyde, which is used as a model system for glucose (Dufrane, et al 1984), aldose reductase, obtained from rat lenses (Inuma et al 1989) and NADPH are incubated at 37 °C. The absorption of NADPH at 340 nm is spectrophotometrically followed for 15 minutes. This decay is proportional to the enzyme activity of aldose reductase, since NADPH and glyceraldehyde react stoechiometrically.

The % inhibition of different sample concentrations can than be calculated with differences in the slopes between sample and blank (without sample). By linearization of the dose response curve (% inhibition in probit against log concentration) the $LC_{50}$ value can be calculated. The $LC_{50}$ value is defined as that concentration of the sample that inhibits aldose reductase with

50%. The data for the herbal extracts was compared to quercitrin, a standard commonly used in aldose reductase inhibition assays. The $LC_{50}$ values for the samples are listed in Table 1.

Table 1

| **Sample** | **$LC_{50}$ (mg/ml)** |
|---|---|
| quercitrin | 0.0004 ± 0.0001 |
| *Chrysanthemum morifolium* | 0.0036 ± 0.0015 |
| *Vaccinium myrtillus* | 0.0045 ± 0.0022 |
| *Buddleia officinalis* | 0.0027 ± 0.0007 |
| *Cistancha salsa* | 0.0160 ± 0.0005 |
| *Glycyrhizza glabra* | 0.0081 ± 0.0028 |

**Formulation example**

An example composition of the preparation is:

| | |
|---|---|
| Pueraria Root extract 5 % | 50 mg |
| Green Tea extract 80 % polyphenols | 20 mg |
| Chrysanthemum morifolium extract 4:1 | 20 mg |
| Vitamin A | 2500 IU |
| Beta-carotene | 2500 IU |
| Lutein | 10 mg |
| Riboflavin | 5 mg |
| Vitamin C | 600 mg |
| Vitamin E | 220 IU |
| Zinc | 15 mg |
| Copper | 3 mg |
| Selenium | 70 µg |
| Bilberry extract | 200 mg |
| Gingko biloba | 30 mg |
| N-acetylcysteine | 200 mg |
| Vitamin B6 | 4 mg |
| Vitamin B12 | 4 µg |
| Folic acid | 600 µg |

## Claims

1. Preparation for the prevention and/or treatment of ocular disorders which comprises
   a. an aldose reductase inhibitor;
   b. an intra ocular pressure lowering component; and
   c. a component that increases ocular blood flow.

2. Preparation according to claim 1, wherein the aldose reductase inhibitor is a *Chrysanthemum morifolium, Bixa orellana Ipomoea batatas, Vaccinium myrtillus, Buddleia officinalis, Cistancha salsa* or *Glycyrhizza glabra* extract.

3. Preparation according to claim 2, wherein the extract from *Chrysanthemum morifolium* comprises acacetin, diosmetin, luteoline or their glucosides and/or ellagic acid.

4. Preparation according to claim 2, wherein the extract from *Bixa orellana* comprises gallic acid and/or pyrogallol.

5. Preparation according to claim 2, wherein the extract from *Ipomoea batatus* comprises scopoletin and/or caffeic acid.

6. Preparation according to claim 1, wherein the aldose reductase inhibitor comprises at least a component selected from the group consisting of acacetin, diosmetin, luteoline, ellagic acid, gallic acid, pyrogallol, isoscutellarein, scopoletin, 3,5-dicaffeoylquinic acid and caffeic acid or their functional analogues, said functional analogues being glucosides, esters or salts thereof.

7. Preparation according to any of the preceding claims, wherein the aldose reductase inhibitor is a *Chrysanthemum morifolium* extract.

8. Preparation according to any of claims 1 to 7, wherein the intra ocular pressure lowering component is a green tea extract.

9. Preparation according to claim 8, wherein the intra ocular pressure lowering component is a catechin, in particular epigallocatechin or epigallocatechin gallate.

10. Preparation according to any of claims 1 to 7, wherein the intra ocular pressure lowering component is myrecetin, quercetin or tannin.

11. Preparation according to any of claims 1 to 10, wherein the component that increases ocular blood flow is an isoflavon or a water soluble carotenoid.

12. Preparation according to claim 11, wherein the isoflavon is puerarin.

13. Preparation according to claim 11, wherein the water soluble carotenoid is crocetin or crocin.

14. Preparation according to any of the preceding claims, comprising

a. Chrysanthemum morifolium extract;

b. green tea extract; and

c. puerarin.

15. Preparation according to any of claims 1 to 14, further comprising lutein.

16. Preparation according to any of claims 1 to 15, further comprising one or more antioxidants.

17. Use of a preparation according to any of claims 1 to 16 for the treatment and/or prevention of ocular disorders.

18. Use of a preparation according to any of claims 1 to 16 for the treatment and/or prevention of cataracts.

19. Use of a preparation according to any of claims 1 to 16 for the treatment and/or prevention of age related macula degeneration.

20. Preparation according to any of claims 1 to 16 for the treatment and/or prevention of glaucoma.

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(71) Applicant (for all designated States except US): N.V. NUTRICIA [NL/NL]; P.O. Box 1, NL-2700 MA Zoetermeer (NL).

(72) Inventor; and

(75) Inventor/Applicant (for US only): VERDEGEM, Peter, Julien, Edward [NL/NL]; Zwanenveld 2413, NL-6538 PA Nijmegen (NL).

(74) Agent: JORRITSMA, Ruurd; Nederlandsch Octroibureau, Scheveningseweg 82, P.O. Box 29720, NL-2502 LS The Hague (NL).

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(54) Title: PREPARATION FOR THE PREVENTION AND TREATMENT OF OCULAR DISORDERS

(57) Abstract: The present invention relates to a preparation for the prevention and/or treatment of ocular disorders which comprises: a. an aldose reductase inhibitor; b. an intra ocular pressure lowering component; and c. a component that increases ocular blood flow. Component a can be *Chrysantemum morifolium, Bixa orellana, Ipomoea batatas Vaccinium myrtillus, Buddleia officinalis, Cistancha salsa* or *Glycyrhizza glabra* extract. Component b can be a green tea extract, myrecetin, querecetin or tannin. Component c can be an isoflavon or a water soluble carotenoid.

# INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61P27/02 A61P27/04 A61P27/06 A61P27/12 A61K35/78

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
PAJ, EPO-Internal, WPI Data, BIOSIS, FSTA, CHEM ABS Data, EMBASE, PASCAL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 10 May 2002 | 03/06/2002 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Skjöldebrand, C |

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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[redacted]

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PCT/GB 01/00348

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1

Present claim 1 relates to a compounds defined by reference to a desirable characteristic or property, namely "aldose reductase inhibitor", an "intraocular pressure lowering component" and a "component that increases ocular blood flow".

Because of the functional definition of claim 1, a full search search over the whole of the claimed scope is impossible, due to the problem of knowing what compounds fall under these definitions. Consequently, the search has been carried out for those parts of the claims relating to the compounds/extracts defined in claims 2-14, as well as keywords relating to the above functional definitions.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

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International Application No
PC[illegible] 01/00348

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